Nonalcoholic fatty liver disease: Updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPAR-γ agonists

Elsevier Editorial System(tm) for Metabolism
Manuscript Draft

Manuscript Number:

Title: Nonalcoholic fatty liver disease: Updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPARγ agonists

Article Type: Editorial

Keywords: hyperlipidemia; metabolic syndrome; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; pioglitazone; PPAR-γ

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Thessaloniki, 2 August 2016

Dear Editor,

We should be glad if you consider our manuscript entitled “Nonalcoholic fatty liver disease: Updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPARγ agonists” for publication in “Metabolism” as an "Editorial".

Our manuscript is an original and previously unpublished work and no other submission or publication of the same material has been or will be made before completion of the review process by “Metabolism” and, in the event the submitted is accepted by “Metabolism”, before its publication.

We also declare that all authors have participated in the study to a significant extent and are in agreement with the content of the manuscript. As requested in the instructions to authors, any conflict of interest is clearly stated in the title page.

Sincerely yours,

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Nonalcoholic fatty liver disease: Updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPARγ agonists

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Running title: NAFLD, Mets and pioglitazone

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Abstract

Not required

Keywords: hyperlipidemia; metabolic syndrome; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; pioglitazone; PPAR-γ.

List of abbreviations: CVD, cardiovascular disease; HOMA-IR, homeostasis model of assessment insulin resistance; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PNPLA, patatin-like phospholipase domain-containing protein; PPAR, peroxisome proliferator activated receptor; RCT, randomized controlled trial; SS, simple steatosis; T2DM, type 2 diabetes mellitus.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a disease of increasing prevalence and has been recognized as a global public health problem, affecting approximately one third of the general adult population and one tenth of children [1,2]. The prevalence of NAFLD increases with obesity, type 2 diabetes mellitus (T2DM) and/or metabolic syndrome (MetS) [1,2]. NAFLD is now among the leading causes of cirrhosis [3], hepatocellular carcinoma [4] and liver transplantation [5]. Besides hepatic morbidity, NAFLD has been associated to extra-hepatic morbidity too [6], including metabolic complications, chronic kidney, malignancies and cardiovascular disease (CVD), which all contribute to the higher mortality observed among NAFLD patients [7]. Specifically, evidence from recent studies strongly emphasizes the importance of assessing the global CVD risk in patients with NAFLD and that NAFLD might be both a marker and an early mediator of CVD.

NAFLD encompasses a spectrum of phenotypes, ranging from nonalcoholic simple steatosis (SS), histologically defined as intrahepatic lipid accumulation with or without mild inflammation, to nonalcoholic steatohepatitis (NASH), characterized by the addition of hepatic necroinflammatory features and/or fibrosis, up to NASH-related cirrhosis and its complications, including hepatocellular carcinoma [8].

The pathogenesis of NAFLD is multifactorial, since various factors ("hits") contribute to its development and progression [9]. Genetic predisposition (e.g., polymorphisms of patatin-like phospholipase domain-containing protein (PNPLA3 gene) [10,11], lifestyle factors (e.g., lack of exercise, high fructose and saturated fat intake etc. [12]), insulin resistance (IR) [13], redox imbalance [14] and certain adipokines [15] are regarded as established "hits", whereas other factors, including impaired innate and adaptive immunity [16], dysbiosis of the gut microbiota [17] and endocrine disruptors [18], have been linked with NAFLD, although further validation is needed.

"*Metabolism, Clinical and Experimental*" has recently published two studies advancing our knowledge in NAFLD, which are presented and commented hereby: one of them focuses on NAFLD association with MetS [19] and the other on NAFLD association

with different types of dyslipidemia [20]. A third study reporting on the long-term efficacy and safety of pioglitazone in NASH patients with T2DM [21], recently published in "*Annals of Internal Medicine*", is also discussed herein.

2. NAFLD and metabolic syndrome

Karajamaki et al. [19] analyzed a subset of data from a cohort study of a middle-aged Finnish population (Oulu Project Elucidating Risk of Atherosclerosis [OPERA] study), aiming to evaluate the dynamic interaction between NAFLD and MetS on left ventricular mass index (LVMI), a surrogate of left ventricular hypertrophy (LVH) and a predictor of cardiac morbidity and mortality in hypertensive patients, major cardiovascular events (coronary heart disease, stroke or death), as well as new incidence of T2DM. More specifically, Karajamaki et al. [19] divided the population at baseline (1991-1993; n=958) into four groups: a) coexistence of NAFLD and MetS (19%); b) NALFD without Mets (7%); c) MetS without NAFLD (17%); and d) neither NAFLD nor MetS (57%). After a mean follow-up of 16.3 years, major cardiovascular events occurred in 30% (hazard ratio [HR]: 2.8; 95% CI: 1.9-3.9), 20% (HR: 1.7; 95% CI: 1.0-3.1), 22% (HR: 2.1; 95% CI: 1.4-3.1) and 12% (reference group), respectively. Interestingly, in a multivariate Cox regression model, MetS with and without NAFLD could predict the risk for cardiovascular events, whereas NAFLD without MetS could not. Change in LVMI was statistically more significant in groups with both NAFLD and MetS, and MetS without NAFLD.

Regarding new cases of T2DM, the rates were 47% (NAFLD and MetS), 24% (NAFLD without MetS), 40% (MetS without NAFLD) and 19% (neither NAFLD nor MetS), being statistically higher in groups with both NAFLD and MetS, and MetS without NAFLD. Interestingly, in the subset of individuals without MetS at baseline, the incidence of MetS during the follow-up was higher in those with (71%) than without (48%) NAFLD. Another important observation of this study is that the unfavorable genotype of *PNPLA3* gene polymorphism, which is strongly associated with the susceptibility and severity of NAFLD [10,11], was most prevalent in individuals with NAFLD without MetS.

To the best of our knowledge, this is the first cohort study evaluating the combined effect of NAFLD and MetS on cardiovascular events and T2DM incidence. Although limited by the fact that OPERA was not specifically designed for this aim and by the small number of individuals in the NAFLD without MetS group (7%), this study indicates that NAFLD affects cardiovascular morbidity and T2DM incidence mainly when it is combined with MetS, thereby implying that IR may be the pathogenetic common denominator resulting in higher cardiovascular morbidity and not NAFLD itself. However, other investigators, also mentioned by the authors [19], reported that hypertensive patients with T2DM and with NAFLD exhibit a remarkably higher frequency of LVH than hypertensive diabetic patients without NAFLD, and that NAFLD is related with LVH independently of conventional cardiovascular risk factors and other potential co-founders [22]. Therefore, due to the limited number of individuals in the NAFLD without MetS group [19], further large-scale relative studies are warranted to elucidate the potential impact of NAFLD on cardiovascular morbidity and T2DM incidence when or not combined with MetS. Furthermore, this study strengthens existing evidence that *PNPLA3* gene polymorphism predisposes to NAFLD, but not MetS or T2DM. In this regard, *PNPLA3* gene polymorphism promotes advanced liver damage in NAFLD [10,11], increasing hepatic morbidity, but it is not associated with IR or T2DM [23], thereby not increasing NAFLD-related cardiovascular morbidity. This study also reinforces the concept that NALFD itself is able to favor the onset of MetS. Therefore, it could be speculated that, when NAFLD is not efficiently managed, it may foster the development of MetS and both of them jointly increase the risk of cardiovascular morbidity. However, this hypothesis should be confirmed by specifically designed future cohort studies.

3. NAFLD and lipid profiles

Du et al. [20] performed a cross-sectional study in a large sample (n=9560) of adult Chinese seen for routine health check-up. Individuals with T2DM or other liver disease and those on lipid-lowering medications were excluded. Based on liver ultrasound examination, approximately 39% of them were diagnosed with NAFLD. Lipid abnormalities were defined

according to National Cholesterol Education Program/Adult Treatment Panel (ATP)-III guidelines [24] and were subdivided into five mutually exclusive categories: a) isolated hypercholesterolemia (high low-density lipoprotein cholesterol [LDL-C], normal triglycerides; 2.9%); b) isolated hypertriglyceridemia (high triglycerides, normal LDL-C and high-density lipoprotein cholesterol [HDL-C]; 13.7%) c) dyslipidemia of MetS (normal LDL-C, low HDL-C, high triglycerides; 9.5%); d) combined hyperlipidemia (high LDL-C and high triglycerides; 2.0%); e) isolated low-HDL-C (low HDL-C, normal LDL-C and triglycerides; 10.9%). Individuals with normolipemia (normal LDL-C, HDL-C and triglycerides; 61.0%) served as a reference group.

Within NAFLD patients, 3.2% had isolated hypercholesterolemia, 23.3% isolated hypertriglyceridemia, 17.7% MetS dyslipidemia, 3.8% combined hyperlipidemia, 10.2% isolated low HDL-C, whereas 41.8% had normolipemia, providing evidence for higher rates of lipid abnormalities in NAFLD. Inversely, all lipid abnormalities showed higher rates of NAFLD compared to individuals with normolipemia (reference group). More specifically, combined hyperlipidemia provided the higher rates (unadjusted odds ratio [OR]: 9.0; 95% CI 6.4-12.7), followed by MetS dyslipidemia (unadjusted OR: 7.30; 95% CI: 6.2-8.5), isolated hypertriglyceridemia (unadjusted OR: 5.3; 95% CI: 4.7-6.1), isolated hypercholesterolemia (unadjusted OR: 2.1; 95% CI: 1.7-2.7) and isolated low HDL-C (unadjusted OR: 1.6; 95% CI: 1.4-1.8). The association between lipid profiles and NAFLD remained robust after adjustment for potential co-founders for combined hyperlipidemia, MetS dyslipidemia and isolated hypertriglyceridemia, but not for isolated hypercholesterolemia and isolated low HDL-C [20].

To the best of our knowledge, this is the largest study evaluating the association between NAFLD and different lipid profiles. Although it is limited by its observational nature, thereby failing to prove causality, and by the fact that lipoprotein (a) (Lp(a)), an independent predictor of cardiovascular risk [25], was not evaluated, this study strengthens our knowledge on the close relationship between NAFLD and lipid profile and its potential impact on CVD. Combined hyperlipidemia also appears to be a risk factor for CDV; high triglyceride levels are associated with increased CVD risk [26] and high LDL-C has now

largely replaced total cholesterol as a risk marker for CVD from a biologic, epidemiologic, and genetic standpoint [27]. Noteworthy, NAFLD remained independently associated with all lipid abnormalities characterized by high triglyceride levels, which is commonly observed in the setting of IR. This study warrants further research. A deeper insight into lipid profiles in patients with NASH, especially those with liver fibrosis who have the poorer prognosis [28], would be of importance, and might have therapeutic perspectives. Implementation of an aggressive therapeutic strategy for dyslipidemia with hypolipidemic agents, also mentioned by the authors [20], might mitigate the risk for CVD among NAFLD patients [29]. However, to-date, contrasting data are available on hypolipidemic treatment in NASH [25,30] but in the end nor omega-3, fibrates or statins clearly proved to be effective in improving the features of liver damage other than steatosis in NASH. On the other hand, another point needing clarification is the selection of medications to treat different lipid profiles specifically in NAFLD subjects. Statins proved to be safe in NAFLD, thereby toning down previous fear for statin use in patients with abnormal liver function tests, while it remains unknown how to treat NAFLD patients with isolated hypertriglyceridemia, MetS dyslipidemia and isolated high HDL-C. Until further studies elucidate this issue in specifically NAFLD populations, it is suggested that we follow the recommendations published for general population.

4. NAFLD and pioglitazone

Cusi et al. [21] performed a single-center, randomized placebo controlled trial (RCT; 18 months) followed by a 18-month open-label extension (totally 36 months) evaluating the long-term safety and efficacy of pioglitazone (45 mg/d; added to a hypocaloric diet), a peroxisome proliferator activated receptor (PPAR)-γ ligand, in patients with diabetes or prediabetes and biopsy-proven NASH (n=101). Previous studies had already shown a favorable effect of pioglitazone on hepatic steatosis and lobular inflammation, whereas its effect on hepatic fibrosis remained unclear, as we recently summarized [31]. At month 18 (end of RCT), more patients in the pioglitazone than in the placebo group (58% vs. 17%, respectively) achieved the primary outcome, being the reduction of at least 2 points in the

NAFLD activity score (NAS) in 2 histologic categories, without worsening of fibrosis [21]. Furthermore, resolution of NASH occurred in 51% of pioglitazone-treated patients vs. 19% of those receiving placebo. Regarding specific histological lesions, patients on pioglitazone improved hepatic steatosis, inflammation, ballooning and, notably, fibrosis more than those in placebo. Interestingly, progression of fibrosis occurred in less patients on pioglitazone (12%) than placebo (28%). As expected, pioglitazone improved hepatic, muscle and adipose tissue IR, liver function tests and circulating adiponectin. All 18-month metabolic and histological improvements persisted over 36 months of therapy (open-label extension). Although weight gain was greater with pioglitazone (mean 2.5 kg over placebo), the overall rate of adverse events did not differ between groups and no case of bladder cancer or osteoporotic fracture was observed in pioglitazone group [21].

This study confirms that long-term pioglitazone treatment in patients with NASH and T2DM or prediabetes is a safe and effective choice and, contrary to previous trials where discontinuation resulted in histological "rebound" [32], it shows for the first time that metabolic and histological improvements, including fibrosis, are maintained during long-term treatment with pioglitazone. Similarly to a previous open-label extension of a rosiglitazone trial in NASH [33], the Cusi et al. study did not show further histological improvement during the extension, a finding that should be cautiously interpreted, because of the open-label nature and relatively high drop-out rates at the end of the extension that possibly resulted in a relatively underpowered substudy.

The pharmacological treatment of NASH remains an unmet medical need [34], but the study by Cusi et al. [21] adds value by proposing the use of pioglitazone in subgroups of NASH patients with T2DM or prediabetes. However, candidates for pioglitazone treatment should be carefully selected because of its potentially adverse effect on CVD, osteoporosis and bladder cancer [31,35]. Notably, selective PPAR-γ modulators have been developed, including INT131 (formerly AMG131) [36]. INT131 is designed to exhibit strong efficacy, but less side effects compared to PPAR-γ full agonists, such as pioglitazone [36]. INT131 was well tolerated and improved glycated hemoglobin in T2DM patients vs. placebo in phase II

trials [37,38]. Less adverse effects, including edema, fluid retention and weight gain were observed compared with rosiglitazone [37] or pioglitazone [38]. Based on these observations, INT131 is one of the most promising candidates for clinical trials in NASH patients, along with other new compounds that are rapidly changing the landscape of the pharmacological treatment of NASH. Noteworthy, pioglitazone, simvastatin or a combination treatment may have synergistic effects by inhibiting different functions, such as inflammatory response and lipid regulation, by inhibiting the CD40-CD40L signaling pathway to suppress the formation of atherosclerosis, and reducing epicardial adipose tissue and plasma inflammatory markers in CVD and MetS patients [39,40]. Specifically, simvastatin, apart from exerting pleiotropic effects on the cardiovascular system, may improve the prognosis of NASH-related fibrosis by increasing the expression of endothelial nitric oxide synthase, decreasing the expression of inducible nitric oxide synthase, and inhibiting the activation of human hepatic stellate cells involved in liver fibrogenesis and carcinogenesis; a low simvastatin dose might have a role in preventing NAFLD and addition of simvastatin is associated with a survival benefit for patients with chronic liver disease [41-43].

5. Closing remarks

NAFLD is a complex disease with a growing prevalence and thus clinical importance affecting both hepatic and extra-hepatic morbidity and mortality. Despite the increasing prevalence of NAFLD, there is currently no definitive therapeutic modality, besides weight loss and exercise [34]. Both, weight loss and exercise, are difficult to achieve and sustain, which makes the need for pharmacological treatment of paramount importance [28]. In our opinion, a more holistic approach might probably lead to more efficient management. NAFLD is not a separate entity: it usually coexists with other components of MetS, including obesity, T2DM and various lipid abnormalities [20], but the cross-talk is probably bi-directional, i.e., NAFLD affects and is affected by other metabolic co-morbidities [44]. For example, T2DM patients have higher prevalence of NAFLD [45], but also hepatic lipid accumulation in NAFLD impairs hepatic glucose and lipid metabolism, thereby increasing the

risk of T2DM and CVD [7]. Because of the multifactorial nature of the disease, a combined treatment, simultaneously targeting more than one pathogenetic "hit", might represent a more realistic management, as we previously suggested [28]. It would be advisable to effectively manage all related comorbidities, i.e., T2DM, lipid abnormalities, arterial hypertension, with a diabetes-like approach [28,46], though the impact on liver damage of such approach is currently unknown and more studies are needed, which however are implicated by the need for repeat biopsies and high drop-out rates [47].

Remarkably, due to its multifactorial nature, the same medications may not be suitable for all NAFLD patients. Du et al. showed the diversity of lipid abnormalities in NAFLD [20], possibly implying that the same hypolipidemic medications are not similarly effective in all NAFLD patients. Further, each NAFLD patient has a different genetic background and different related co-morbidities and, last but not least, each patient has a different time course of liver disease, often unpredictable. Therefore, beyond the search for the single, "magic bullet" medication, suitable for all NAFLD patients, research should be oriented to a more holistic approach and a more personalized management.

Acknowledgements: None

Conflict of interest

SAP: consulting fees from InteKrin Therapeutics Inc.

EB: consulting fees for Genfit, Intercept, IBSA.

JK: None

CSM: consulting fees from InteKrin Therapeutics Inc; shareholder of Coherus Biosciences Inc.

Financial disclosure: No funding or financial support for this manuscript.

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